DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: AUG - 1 2005

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Ubiquinol

Firm: KANEKA

Date Received by FDA: 5/5/05

90-Day Date: 8/3/05

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Lutwak

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

JUL 19 2005

David H. Bechtel, Ph.D.
Senior Scientific Consultant
CANTOX U.S. Inc.
1011 U.S. Highway 22, Suite 200
Bridgewater, NJ 08807

Dear Dr. Bechtel:

This is to inform you that the notification, dated April 28, 2005, that you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on May 5, 2005. Additional information that you sent, dated June 20, 2005, was received by the Agency on June 21, 2005. Your notification was submitted on behalf of your client, Kaneka Corporation and concerns the substance that you call "ubiquinol" or "KANEKA QH™" that they intend to market as a new dietary ingredient.

According to the notification you intend to market your new dietary ingredient "ubiquinol" in softgel capsule form. The notification states that "each serving of the dietary supplement will contain 50 mg of KANEKA QH™. Consumption of up to 6 servings per day will be suggested or recommended in the label directions."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "ubiquinol" will reasonably be expected to be safe.

Your notification included data and information which you relied on to determine that 50 mg six (6) times per day of your new dietary ingredient, "ubiquinol", is safe for chronic human consumption. Your notification included the results of a 13-week study in rats gavaged with doses of 300, 600 or 1200 mg/kg "ubiquinol". Based on the results submitted, you concluded that the no observed adverse event levels (NOAELs) for male and female rats were 600 mg/kg/day and 300 mg /kg/day, respectively. Your notification also included the results of a 13-week study in beagle dogs gavaged with 150, 300 and 600mg/kg /d of "ubiquinol". You reported abnormal hematology levels in beagle dogs as a result of "ubiquinol" consumption, low eosinophils in males at the150 and 600 mg/kg doses; low platelets in females at week 13 at the 300 mg/kg; dose and high neutrophils in males at week 7 at the 600 mg/kg dose. In addition you reported abnormal blood chemistry levels in beagle dogs as a result of "ubiquinol" consumption, low potassium in females at week 7 at the 150 and 300 mg/kg doses, low total protein females at weeks 7 and 13 at the 150 mg/kg dose, low A/G ratio in males at weeks 7 and 13 at the 600 mg/kg dose; and abnormal AST, ALT, LDH levels at week 13 in females at the 300 mg/kg dose. You also reported abnormal electrocardiography parameters in beagle dogs as a result of "ubiquinol" consumption: low heart rates and prolonged PR intervals (first degree atrio-ventricular block) at weeks 7 in males and 13 in females at the 300 and 600 mg/kg dose, respectively.

In addition, your notification included descriptions of clinical studies conducted with ubiquinone, the oxidized form of your proposed new dietary ingredient, "ubiquinol". Your notification included published references which support the rapid conversion of ubiquinone to ubiquinol in most tissues. However, it is not clear to FDA how the clinical data and information about ubiquinone support the safety of "ubiquinol".

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that the dietary supplement product containing "ubiquinol", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of May 5, 2005. After the 90-day date, the notification will be placed on public display at FDA's Division of Docket Management in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Linda Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
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Center for Food Safety
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CTS 91510
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April 28, 2005

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FDA / VL

Dr. Susan J. Walker
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling,
and Dietary Supplements
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740-3835

RE: FDA Response Letter for New Dietary Ingredient Notification (KANEKA QH™ Brand of Ubiquinol)

Dear Dr. Walker:

I received your letter of February 10, 2005 concerning the Agency's review of the New Dietary Ingredient (NDI) notification for KANEKA QH™ brand of ubiquinol. The original NDI notification, dated December 2, 2004, included summaries of the information forming the basis of our conclusion that the substance does not pose an unreasonable risk of harm. The agency indicated in the letter of February 10, 2005 that it had concerns about the evidence upon which this conclusion was based. In a conference call between representatives of FDA (Linda S. Pellicore, Ph.D and Ms. Vickey Lutwak) and Kaneka representatives on March 7, 2005, specific areas considered to be deficient in the original application were identified.

Pursuant to that discussion, CANTOX respectfully submits a new, amended NDI for KANEKA QH™ brand of ubiquinol. Enclosed is the complete version of this notification, in which additional information and clarification is provided to address the previous concerns of the Agency. In addition, an overview of these changes is provided herein and a red-lined version highlighting these changes is included as an attachment.

Dr. Pellicore requested additional clarification and information related to the following:

1. The composition of and specifications for "Coenzyme Q_{10} (KANEKA Q-10™)," the raw material for KANEKA QH™ and the methodology used to determine that Coenzyme Q_{10} meets such specifications.

2. Additional information related to the methodology for measuring the ubiquinol content of various foods "using high-performance liquid chromatography (HPLC) with an electro chemical detector."

3. Supporting genotoxicity data, and specifically, support for the statement that "in the presence of S9, the incidence of cells with structural chromosomal aberrations and polyploidy cells in the groups treated with ubiquinol were similar to those in the negative control group."

4. An explanation of the various names used to identify test materials in the published studies and clarification of the relationship between these materials used in the published studies and KANEKA QH™.

5. A statement added to the conclusion that KANEKA is safe for long-term (*i.e.*, chronic) use with general references to the supporting data.

In addition to these items discussed during the March 7th conference call, the agency indicated in the letter of February 10, 2005 that the original notification failed to provide sufficient information related to the composition and manufacturing process for KANEKA QH™.

The following are responses to each of the areas identified above; the amended NDI submitted herewith reflects these responses in greater detail.

1. [redacted]

2. [redacted]

3. [redacted]

4. [redacted]

5. The following statement was added to the conclusion:

   Based on the evidence above, including results of chronic safety studies, the absence of mutagenic and reproductive activity, the presence of a safety factor in excess of 100-fold for human exposure compared to the lowest effect levels in safety studies, and substantial clinical experience indicating ample tolerance as well as potential benefit, KANEKA concludes that the chronic use of KANEKA QH™ in dietary supplements at a level of up to 300 mg KANEKA QH™ (equivalent to 6 mg/kg/day for a 50 kg body weight person), will be reasonably expected to be safe (page 71).

6.

Having provided these clarifications to address the specific concerns of the agency, CANTOX and Kaneka reaffirm their original assertion that a dietary supplement containing KANEKA QH™ brand of ubiquinol would reasonably be expected to be safe when used according to the conditions of use recommended or suggested in the labeling of the dietary supplement.

On behalf of Kaneka Corporation, CANTOX hereby confirms that this letter and the enclosed Notification contain trade secret or otherwise confidential commercial information which should not be disclosed to the public pursuant to 21 C.F.R. §§20.61 and 190.6(e). More specifically, the Notification contains valuable data and information which Kaneka Corporation has held in strict confidence and has not disclosed to any member of the public. If it would assist the staff, CANTOX or Kaneka will submit redacted copies of this letter and Notification, specifically identifying such confidential and proprietary information.

We respectfully submit that the revised notification fully responds to the Agency's concerns and is consistent with the discussion during the March 7, 2005 conference call with the Agency staff. We appreciate the staff's input and hope that the revised submission will facilitate the staff's prompt review of the revised Notification.

Respectfully,

David H. Bechtel, Ph.D., DABT
Managing Director & Sr. Scientific Consultant

Enclosures